TAB 5

1526.100A PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	Examiner: P.K. Sripada
HARALD BREIVIK, ET AL.	)	Group Art Unit: 1202
Serial No.: 07/902,500	)	
Filed: June 23, 1992	)	
For: FATTY ACID COMPOSITION	)	

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION OF
WILLIAM E. CONNOR, M.D., AND LAUREN HATCHER, M.S., R.D.

Sir:

William E. Connor, M.D., and Lauren Hatcher, M.S., R.D., do hereby declare as follows:

1) Dr. Connor is a medical doctor and a Professor with the Division of Endocrinology, Metabolism and Clinical Nutrition at the Oregon Health Sciences University, Portland, Oregon.

2) Ms. Hatcher is a Registered Dietician in the Clinical Research Center of the Oregon Health Sciences University.

3) During 1988, Dr. Connor and Ms. Hatcher, together with Dr. Arne Nordøy and Ms. Louise Barstad, conducted a clinical study at Oregon Health Sciences University of a new omega-3 fatty acid fish oil concentrate, known as "K-85,"

that was sent to the United States from Norway for purposes of the study. The following paragraphs summarize work done on the study, all of which took place in the United States.

4) On February 1, 1988, one thousand capsules of a mixed-fatty-acids composition containing 85.6 weight percent of a combination of (all-Z omega 3)-5,8,11,14,17-eicosapentaenoic acid (EPA) and (all-Z omega-3)-4,7,10,13, 16,19-docosahexaenoic acid (DHA), in a weight ratio of EPA: DHA of 1.33, were received by Dr. Nordøy at Oregon Health Sciences University ("OHSU") for purposes of testing, to see if the EPA and DHA components of the composition would be adequately absorbed into the human bloodstream. The capsules were sent by Dr. Knut Dahl, of Norsk Hydro a.s, in Porsgrunn, Norway. The fatty acids were present in the composition in the form of ethyl esters. Dr. Nordøy, a native of Norway, was a visiting Professor of Clinical Pathology and Medicine at OHSU at the time. The product, dubbed "K85", was analyzed in the University's Lipid-Atherosclerosis Laboratory. As evidenced by the attached Exhibit A, which is a copy of the analysis sheet, the analysis indicated that the capsules contained the following composition:

Fatty Acid	Weight Percent of Total Fatty Acids
16:1n-7	0.5
18:1n-9	0.2
19:0	0.2
18:2n-6	0.5

18:3n-6	0.2
18:3n-3	0.4
18:4n-3	3.2
20:4n-6	1.9
20:4n-3	1.9
20:5n-3 (EPA)	48.8
22:4n-6	2.5
22:5n-6	0.1
22:5n-3	2.2
22:6n-3 (DHA)	36.8
Saturated	0.3
Monounsaturated	0.7
Polyunsaturated	98.9
n-9	0.2
n-6	5.4
n-3	93.5
EPA + DHA	85.6
EPA/DHA wt. ratio	1.33

5) It was agreed that the University's Clinical Research Center would conduct a clinical study involving the product received from Dr. Dahl, and that the results would be provided to Dr. Dahl. There were four investigators on the study: Dr. Nordøy, Dr. William E. Connor, Ms. Lauren Hatcher, and Ms. Louise Barstad. Dr. Nordøy was the principal investigator, until his return to Norway on June 24, 1988, when Dr. Connor took over that responsibility. Ms. Hatcher

was the dietitian for the study, ~~and the organizer of the data~~. Ms. Barstad was the principal biochemical analyst on the study.

6) The study involved the withdrawal of blood from each of six fasting volunteers, followed by oral administration of the test composition with a formula breakfast, and then collection of venous blood samples at intervals of 2 hours, 4 hours, 6 hours, 8 hours, and 24 hours after ingestion. The chylomicrons fraction was extracted from each of the blood samples and analyzed in the University's Lipid-Atherosclerosis Laboratory for its fatty acid content, including the levels of EPA and DHA specifically. The plasmas of the initial (0-hour) and 24-hour blood samples were also analyzed for fatty acid content, including levels of EPA and DHA, in four different fractions of the plasma: phospholipids, cholesterol esters, triglycerides, and free fatty acids. Plasma cholesterol, triglyceride, and lipoprotein lipid concentrations were also measured. In all, approximately 350 different sample fractions were analyzed.

7) Each of the study participants was given the K-85-containing meals on two different days, with and without a supplement of olive oil. The olive oil was added to keep the total lipid content comparable to the other meals. For comparison, each of the test subjects was also given meals with added olive oil alone, or with fish oil concentrate

containing only 55 wt.% of EPA+DHA, in triglyceride form. Those, of course, were on different days. There were a total of four treatment days for each of the participants, spread far enough apart to avoid overlapping effects.

8) The investigators worked diligently on the study from at least as early as March 1, 1988, until at least as late as August 11, 1988. The following is a complete listing of all of the administrations:

EE = Claimed Composition (i.e., K85 (85.6% EPA+DHA) in ethyl ester form)

OO = Olive Oil

TG = 55% EPA+DHA, in triglyceride form

TABLE I

Date	Subject 1	2	3	4	5	6
March 1, 1988	EE+OO					
March 16, 1988	TG	EE+OO	EE+OO			
March 29, 1988	OO	TG				
April 4, 1988			TG	EE+OO		
April 18, 1988	EE	OO				
April 25, 1988			OO	TG		
May 3, 1988		EE				
May 10, 1988			EE	OO		
May 17, 1988				EE	EE+OO	
May 23, 1988						EE+OO
May 26, 1988					OO	OO
May 31, 1988					TG	TG

June 8, 1988 EE EE

June 21, 1988 EE+OO

9) Chromatographic analyses of the various blood fractions were performed as soon as time permitted. Of the total of some 350 different analyses, Table II lists the dates of just a small portion, including what may have been the last of the analyses, on July 8:

TABLE II

Analysis Date	Blood Sample Date	Times of Samples	Blood Fraction
June 9, 1988	May 17 & 18, 1988	0 & 24 hr	Plasma TG, CE, & PL
June 14, 1988	May 17 & 18, 1988	0 & 24 hr	Plasma FFA
June 17, 1988	May 17, 1988	0 hr	Chylomicron
June 18, 1988	May 17 & 18, 1988	2, 4, 6, 8 & 24 hr	Chylomicron
June 30, 1988	June 21 & 22, 1988	0 & 24 hr	Plasma
July 8, 1988	June 21 & 22, 1988	0, 2, 4, 6 8 & 24 hr	Chylomicron

Attached as Exhibit B are copies of some of the notebook entries recording dates of various blood withdrawals and some of the blood data obtained. The dates are entered in European style -- "1/3" means March 1; "17/5" means May 17, etc.

Attached as Exhibit C are copies of some of the chromatographic analysis reports. In these reports the dates are entered in the American style -- "5/17" means May 17, etc.

10) After the last of the biochemical measurements on the blood samples was completed, it was Ms. Hatcher's responsibility to organize the data for Dr. Nordøy. As evidenced by the attached Exhibit D, which is a copy of Ms. Hatcher's Time and Attendance Record for her work at the University during July 1988, Ms. Hatcher took the first week of her summer vacation from July 11 through July 15, 1988. Upon her return, she worked diligently to complete the organization of the test diet composition data, and she mailed the results to Dr. Nordøy on July 28, 1988 (a Thursday). Attached as Exhibit E is a copy of her cover letter. During July and August, Ms. Hatcher consulted periodically with Dr. Connor, at the University, about the completion of the study. These meetings occurred at least on July 6 and 29, and August 2, 1988. As evidenced by the attached Exhibit F, which is a copy of Ms. Hatcher's Time and Attendance Record for the month of August 1988, on August 3, 1988, Ms. Hatcher began the rest of her summer vacation, which lasted until the afternoon of August 12. As evidenced by the attached Exhibit G, which is a copy of Dr. Connor's appointment calendar for August 1988, Dr. Connor took one week of vacation during this same period, from August 7 through August 13. Thereafter, still further work was done at the University in connection with the study, e.g., statistical analyses of the data.

11) During the period from March 1, 1988, to August 11, 1988, the investigators were working on approximately five other clinical studies as well. In addition, Dr. Connor was

fulfilling his responsibilities as a care provider for patients at the University's Lipid Clinic and as a teacher in the University's Department of Medicine.

———— • ————

Each of the Undersigned declares further that all statements made herein of his or her own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-captioned patent application or any patent issuing thereon.

William E. Connor, M.D.

Date of Execution: May 23, 1995

Place of Execution: Portland, Oregon

Lauren Hatcher, M.S., R.D.

Date of Execution: May 23, 1995

Place of Execution: Portland, Oregon

F501\W92736\JWB\zrg

RESPONSE UNDER 37 CFR 1.116
EXPEDITED PROCEDURE
EXAMINING GROUP 1202

1526.100A PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	:Examiner: P.K. Sripada
HARALD BREIVIK, ET AL.	:Group Art Unit: 1202
Serial No.: 07/902,500	
Filed: June 23, 1992	
For: FATTY ACID COMPOSITION	

Assistant Commissioner for Patents
Box AF
Washington, D.C. 20231

DECLARATION OF HARALD BREIVIK ET AL.
UNDER 37 C.F.R. § 1.131

Sir:

1) We, the undersigned, are the applicants in the above-identified patent application (hereinafter "this application").

2) We conceived the invention claimed in this application in Norway, and prior to May 26, 1988, the invention was communicated to Dr. Arne Nordøy, who, from July 1987 through June 1988, was a Visiting Professor of Clinical Pathology and Medicine at Oregon Health Sciences University ("OHSU") in Portland, Oregon, U.S.A.

3) On January 29, 1988, one of us (namely, Knut H. Dahl) sent one thousand capsules of a mixed-fatty-acids composition containing a combination of (all-Z omega 3)-5,8, 11,14,17-eicosapentaenoic acid (EPA) and (all-Z omega-3)-4, 7,10,13,16,19-docosahexaenoic acid (DHA), in a weight ratio of EPA:DHA that was within the range of 1:1 to 2:1, to Dr. Nordøy, at OHSU, for purposes of testing to see if the EPA and DHA components of the composition would be adequately absorbed into the bloodstream in man. Dr. Dahl was acting on behalf of our employer, Norsk Hydro a.s, which is the assignee of all our rights in this application. The fatty acids were present in the composition in the form of ethyl esters. As analyzed in Norway, prior to encapsulation, the composition had a combined EPA+DHA content of 83.4 wt.%. The capsules arrived at OHSU on February 1, 1988.

4) It was agreed that OHSU's Clinical Research Center would conduct a clinical study involving the K-85 capsules, and that the results would be provided to Dr. Dahl. We were advised by Dr. Nordøy that the investigators on the study would be himself, William A. Connor, M.D., Professor of Medicine, Division of Endocrinology, Metabolism and Nutrition, OHSU Department of Medicine, and Lauren Hatcher, M.S., R.D., Research Dietitian in the OHSU Clinical Research Center. At Dr. Dahl's request, Dr. Nordøy signed a secrecy agreement regarding some of the information about K-85 that was supplied to him by Dr. Dahl. Also, it was agreed that

Norsk Hydro a.s would have the right to use the data from the Oregon study, and that the investigators would not publish the results before giving Norsk Hydro the opportunity to review the manuscript.

5) The study was performed substantially as agreed upon, and the results were communicated to us by Dr. Nordøy, also as agreed upon.

We the undersigned declare further that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true, and, further, that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or of any patent issuing thereon.

Date: 18.5.95 — Harald Breivik

Date: 15/5-95 — Bernt Borretzen

Date: _____ — Knut H. Dahl

Date: _____ — Hans E. Krokan

Date: _____ — Kaare H. Bonaa

F501\W92742\JWB\zrg\jjr